REMARKS

The Restriction and Election of Species Requirements

Both a restriction requirement and an election of species requirement had previously been entered.

The Restriction Requirement. For the reasons given in detail in the Applicants' May 21, 2007 Response, it is respectfully submitted that the restriction requirement should either be withdrawn, or re-characterized as an election of species requirement. Applicants reserve the right to re-present the canceled subject matter at a later date. Applicants also reserve the right to file a petition for review of the final restriction requirement.

However, in the interest of expediting prosecution, the Applicants had previously amended the Claims to be consonant with Group I as identified in the Restriction Requirement.

The Election of Species Requirement. The Office has held Claims 6, 10, 11, 17, 21, and 22 to be withdrawn as being directed to non-elected inventions. For the reasons given below, it is respectfully submitted that the examined claims are in condition for allowance.

Once the elected claims have been allowed, it then follows that the non-elected Claims should be rejoined and fully examined in the present application as well. In particular, the Office's attention is respectfully directed to M.P.E.P. §§ 821.04 and 821.04(a), which provide for rejoinder of the non-elected Claims in such a case.

Note particularly that rejoinder under M.P.E.P. §§ 821.04 and 821.04(a) does not depend upon whether the original election was made with or without traverse.

Claim 13 Properly Belongs in Group I, and Should Now be Examined.

Applicants respectfully traverse the Office's new proposed restriction of Claim 13 from the rest of Group I.

The March 20, 2008 Office Action asserted that Claim 13 had been amended in a manner that made it independent or distinct from the rest of Group I, and accordingly held that Claim 13 was withdrawn from further consideration as being directed to a non-elected invention.

It is respectfully submitted that amended Claim 13 is properly part of Group I, and that Claim 13 should continue to be examined with the rest of Group I, as it had been in the first action on the merits. There are two independent, alternative reasons for this conclusion: **(1)** Amended Claim 13 is, in fact, consonant with Group I as defined in the original restriction requirement. **(2)** The Office has not given even a *prima facie* basis for restricting Claim 13 from the rest of Group I. For either of these reasons, Claim 13 should be rejoined and should again be examined along with the rest of Group I.

(1) Amended Claim 13 is consonant with Group I. The scope of amended Claim 13 is similar (though not identical) to that of Claim 14 as originally filed. The Office had classified original Claim 14 in Group I. What differences do exist between amended Claim 13 and original Claim 14 bear no relationship to the rationale upon which the Office had restricted Group I from Group II. Amended Claim 13 should be placed in Group I for the same reasons that original Claim 14 was placed in Group I.

The Office characterized Group I as "drawn to a method of preventing or inhibiting infection by the human immunodeficiency virus by administering a porphyrin macrocycle of formula I . . . ." The Office characterized Group II as "drawn to a method of preventing or inhibiting infection by a virus other than the human immunodeficiency virus by administering a porphyrin macrocycle of formula I . . . ."

While the Applicants do not agree with the Office's characterization of the two Groups in all respects, what is clear is that the only difference that the Office identified between the two Groups was whether a claimed method was directed to preventing or inhibiting infection by: (I) the human immunodeficiency virus, or (II) a virus other than the human immunodeficiency virus.

Amended Claim 13 is directed to a "method for killing the human immunodeficiency virus in or on a nonliving material . . . ." Of the two Groups that the Office has defined, one

concerns HIV and one concerns viruses other than HIV. Amended Claim 13 is expressly directed against HIV, and therefore belongs with Group I.

(2) The Office has not given a *prima facie* basis for restricting Claim 13. With all respect, the Office has not given even a *prima facie* basis for restricting Claim 13 from the rest of Group I. It is always the Office's burden to justify a proposed restriction requirement. Where the Office has presented not even a *prima facie* case for restriction, then restriction may not properly be required, and the restriction requirement must be withdrawn.

On some initial procedural points, the Office has not provided a "clear and detailed record of the restriction requirement to provide a clear demarcation between restricted inventions . . . ." See M.P.E.P. § 814, first paragraph. Likewise, the Office has not (1) identified each group, nor (2) listed the claims in each group, nor (3) given a short description of the subject matter in each group, nor (4) classified each group. Each of these four items is required in a proper restriction requirement. See M.P.E.P. § 817, under the heading "Outline of Restriction Requirement," subpart (A). The Office evidently contends that amended Claim 13 is not part of Group I. But the Office has identified no other Group into which Claim 13 belongs. It is clearly not part of Group II, since Group II concerns viruses other than HIV. But the Office has defined no other Groups. Thus the proposed restriction of Claim 13 from the rest of Group I is plainly deficient on its face.

Furthermore, even if the Office were to remedy these procedural omissions, i.e., to better define the scope of the proposed new restriction requirement, that alone would not justify the new restriction requirement. There are two separate criteria that must both be satisfied for a restriction requirement to be proper:

(1) The inventions must be independent or distinct as claimed;

and

(2) There must be a serious burden on the examiner if restriction is not required.

M.P.E.P. § 803, part I.

Nothing in the March 20, 2008 Office Action addresses either of these two mandatory criteria. In fact, the only substantive remark in the Office Action that purported to compare the respective scope of Claim 13 to that of Group I was the following:

> Claim 13, drawn to a method for killing HIV in or on a nonliving material by administering a porphyrin macrocycle of formula I, has been withdrawn as it does not read on the elected invention.

March 20, 2008 Office Action, p. 2, par. 2.

Even if this assertion were accurate in all respects,[1] it still would not address either of the two mandatory criteria that must be present to justify a restriction requirement. The burden is on the Office to demonstrate: **(1)** that one or more of the criteria of M.P.E.P. Chapter 800 is satisfied, to show that the inventions are independent or distinct as claimed; and **(2)** that there would be a serious burden on the examiner if restriction were not required. The quoted statement addresses neither of the two mandatory criteria.

Additionally, see also M.P.E.P. § 811, second paragraph: "Before making a restriction requirement after the first action on the merits, the examiner will consider whether there will be a serious burden if restriction is not required." Because Claims 13 and 14 as originally presented have already been searched and examined, and because the scope of amended Claim 13 is similar (though not identical) to the scope of Claim 14 as originally filed, it is respectfully submitted that there will be no serious burden if restriction of Claim 13 is not required. Even if, for sake of argument, one assumed that Claim 13 might otherwise properly have been restricted from Group I before a first action on the merits (and it is respectfully submitted that is not the case), it is respectfully

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[1] For the record, Applicants do not agree that the Office's characterization of Claim 13 is accurate in all respects.

submitted that there would nevertheless be no serious burden on the Examiner to continue to examine Claim 13 on the merits after original Claims 13 and 14 had been searched and examined. M.P.E.P. § 811 cautions that restriction requirements after a first action on the merits should be carefully considered, and should not be automatic.

It is respectfully submitted that the new restriction requirement respecting Claim 13 should be withdrawn, and that Claim 13 should be examined on the merits along with the rest of Group I.

The § 112, Second Paragraph Rejection

Claims 8 and 19 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite respecting the limitations concerning the wavelength, intensity, and duration of light exposure. It is respectfully submitted that these functional limitations are definite, and comply with § 112, second paragraph.

The January 10, 2008 Amendment at pp. 5-6 explained in detail that functional limitations are generally acceptable in patent claims, and explained in particular why the functional language used in Claims 8 and 19 is acceptable. In the interest of brevity, that discussion will not be repeated here. Please see the earlier discussion if there are any questions concerning the acceptability of functional language in Claims.

If the undersigned has correctly understood the Office's response (March 20, 2008 Office Action, p. 4, 1st par.), it appears that the Office is not questioning the use of functional language *per se*. Instead, the Office has asserted that "undue experimentation" would be needed "to determine these suitable parameters in the context of treatment of HIV infection." It is respectfully submitted that this basis for rejection is misplaced, for either of two separate reasons: **(1)** There is no direct or necessary relationship between degree of experimentation and the clarity of a claim. **(2)** In any case, the degree of experimentation required here is only routine.

(1) There is no direct or necessary relationship between degree of experimentation and the clarity of a claim. It should be kept in mind that a claim is definite if its scope is clear. If the metes and bounds of a claim are clearly ascertainable,

then the claim, no matter how broad, may not properly be rejected under § 112, second paragraph. As stated by the Court of Customs and Patent Appeals, one of the predecessor courts to the Court of Appeals for the Federal Circuit, if each of the limitations of a claim is definite, then the claim is definite and may not be rejected under section 112, second paragraph. *In re Goffe*, 526 F.2d 1393, 1397-98; 188 USPQ 131, 135 (CCPA 1975).

The limitation in question from amended Claim 8 reads as follows:

> exposing tissue of the patient to light having a wavelength, intensity, and duration sufficient to significantly enhance the compound's treatment of viral infection.

(The corresponding limitation from Claim 19 is similar, though not identical.)

The words in a patent claim should be interpreted as they would be understood by a person of ordinary skill in the art. A person of ordinary skill in the art would readily understand the concepts of exposing tissue to light, using a suitable wavelength of light to enhance the treatment, using an intensity of light that will enhance the treatment, and employing a duration of light exposure that will enhance the treatment. The claim limitations are clear. Section 112, second paragraph requires no more.

(2) The degree of experimentation required is only routine. There is no direct or necessary relationship between degree of experimentation and the clarity of a claim. However, in the interest of accelerating prosecution, some brief remarks will now be given as to why, in any event, there would be no undue experimentation. Given the teachings of the present specification, a person of ordinary skill in the art would readily understand the concepts of exposing tissue to light, finding a suitable wavelength of light to enhance the treatment, finding an intensity of light that will enhance the treatment, and finding a duration of light exposure that will enhance the treatment. The degree of testing required can only be considered routine. To paraphrase slightly, the questions are: "What color light should be used? How bright should it be? How long should the light stay on?" Photodynamic therapy is an established field. To answer questions such as these would

be considered routine to those of ordinary skill in photodynamic therapy, and would not require undue experimentation.

§ 112, Second Paragraph Summary. The Claims are definite. There is no direct or necessary relationship between degree of experimentation and the clarity of a Claim. Furthermore, even if the degree of experimentation were a proper factor to consider, the degree of experimentation that would be required in this case would be routine for a person of ordinary skill in the art. It is respectfully submitted that the § 112, second paragraph rejection should be withdrawn.

The § 103 Rejection

Claims 1, 4, 5, 7-9, 12, 15, 16, 18-20, and 23 were rejected under 35 U.S.C. § 103(a) as being obvious over a proposed combination of Debnath *et al.*, "Anti-HIV-1 activity of carborane derivatives of porphyrins," *Med. Chem. Res.*, vol. 9, pp. 267-273 (1999) and Vicente *et al.*, WO 01/85736.

It is respectfully submitted that there would have been no motivation to make the proposed combination of references. Nor would there have been a reasonable expectation of success, even if one assumed for the sake of argument that some hypothetical motivation might have existed to combine the references (and there would have been no such motivation).

Reasons why there would have been no motivation to make the proposed combination of references were discussed in the January 10, 2008 Amendment at pp. 7-9. Those reasons are still valid, but will not be repeated here in the interest of brevity. The Office is respectfully requested to review those reasons in conjunction with the present discussion.

The present discussion will instead focus on why there would have been no reasonable expectation of success – even if one were to assume, hypothetically, for the sake of argument, that some motivation might have existed to make the proposed combination of references.

It is respectfully submitted that at a key point, the March 20, 2008 Office Action impermissibly attempted to shift the burden of persuasion from the Office to the Applicants. In summary, there is an area of substantial uncertainty in the prior art. This uncertainty means that there could have been no reasonable expectation of success, even had one of ordinary skill in the art (hypothetically) found some motivation to combine the references, as an experiment that might be considered "obvious to try." The Office Action, however, treated this area of uncertainty precisely backwards. The Office Action asserted that the uncertainty in the prior art was irrelevant, because the Applicants had not established what effect it might or might not have on the claimed method of treatment.

With all respect, the Office's rationale was exactly backwards. It is precisely because there is a substantial area of uncertainty that there could have been no reasonable expectation of success. If one could have reasonably predicted what effect this factor might or might not have, then perhaps the uncertainty could have been removed. But that is not the case here. Once an area of substantial uncertainty has been identified in the prior art, it is not the Applicants' burden to show what its effect might be. Rather, it is the Office's burden to show why the proposed combination would have had a reasonable expectation of success, despite the presence of the uncertainty.

More specifically, for purposes of this discussion it will be assumed (strictly for the sake of argument) that some motivation might have existed to make the proposed combination of Debnath and Vicente. (For the reasons given in the January 10, 2008 Amendment, it is respectfully submitted that there would have been no such motivation, and Applicants reserve the right to argue this point in the future, should the need arise.) Even if one makes this assumption, however, there still would have been no reasonable expectation of success.

The following thirteen points from the January 10, 2008 Amendment (pp. 7-9) were not questioned by the March 20, 2008 Office Action. Applicants therefore assume that the Office agrees with each of the following:

(1) Debnath and Vicente addressed different problems, and employed different classes of chemical compounds.

(2) Debnath teaches that certain ester-linked carborane derivatives of porphyrins have activity against HIV. In each of Debnath's compounds, the carboranyl groups were linked to the porphyrin macrocycle via ester linkages.

(3) By contrast, independent Claims 1 and 13 each require "one or more carboranyl groups that are linked to the porphyrin macrocycle by carbon-carbon bonding."

(4) Debnath neither teaches nor suggests the use of any compounds in which carboranyl groups are linked to a porphyrin macrocycle by carbon-carbon bonding.

(5) Debnath's ester linkages are susceptible to hydrolysis.

(6) By contrast, the carbon-carbon bonds linking the boron-containing groups to the porphyrin macrocycle in the compounds used in the claimed inventions are highly resistant to hydrolysis.

(7) Nothing in Debnath suggested that susceptibility to hydrolysis could be a problem, nor that susceptibility to hydrolysis would have been undesirable.

(8) Vicente discloses compounds in which carboranyl groups are linked to a porphyrin macrocycle by carbon-carbon bonding.

(9) Vicente taught the use of the disclosed compounds for a very different purpose, namely, as neutron capture agents for cancer therapy. Nothing in Vicente suggested using the disclosed compounds as antiviral drugs.

(10) When compounds such as those disclosed by Vicente are used as neutron capture agents for cancer therapy, the advantages of resistance to hydrolysis are straightforward. The mechanism of action is relatively well-understood, and involves a well-characterized nuclear reaction. A boron-10 nucleus captures a low-energy neutron to become boron-11, which subsequently fissions into an alpha particle and a lithium ion:

$$^{10}B(n, alpha)^{7}Li$$

Both the alpha particle and the lithium ion cause damage to tumor cells in close proximity, through ionization processes. Thus there is a clear advantage to being able to deliver large numbers of boron atoms to tumor cells. It would be a distinct disadvantage to non-selectively lose a significant fraction of the boron atoms to the rest of the body through hydrolysis.

(11) In the context of neutron capture therapy, knowledge of the mechanism of action allows one to predict with some confidence that resistance to hydrolysis

should be an advantage, as such resistance will help retain boron atoms in the vicinity of the tumor, and reduce unwanted side effects in non-target tissues.

(12) By contrast, the antiviral mechanism of porphyrin compounds is not understood, certainly not at the same level of detail as the ^{11}B nuclear fission reaction. On page 267, Debnath describes a proposed mechanism that involves binding of the compounds to the V3 hypervariable loop of the HIV gp120 envelope glycoprotein. However, even if the proposed mechanism is correct, it does not provide the same level of detail, nor the same predictive power as does knowledge of the ^{11}B nuclear fission reaction in neutron capture therapy. While it is straightforward to expect that retention of the carboranyl groups is an advantage for neutron capture-based ionization therapy of tumors, it is much harder to predict whether antiviral activity, or binding to the V3 hypervariable loop of the HIV gp120 envelope glycoprotein, would be helped or hindered by hydrolysis of the ester groups to release free carboranyl groups.

(13) Nothing in either Debnath nor Vicente suggests any answer to this question. Perhaps hydrolysis of the carboranyl groups enhances antiviral activity. Perhaps hydrolysis is essential to antiviral activity. Perhaps preventing such hydrolysis via carbon-carbon bonding would diminish antiviral activity. Perhaps preventing such hydrolysis would destroy antiviral activity. The cited references neither address this question, nor suggest any answer to it.

Unless the undersigned has misinterpreted the Office's remarks, it appears that the Office has not disputed any of these points. If that is not the case, then the Office is respectfully requested to clarify any disagreement that the Office may have with any of these points.

There would have been no way to predict, with any reasonable degree of certainty, whether antiviral activity would be enhanced, diminished, or even abolished by linking carboranyl groups to a porphyrin macrocycle such that the linkage is resistant to hydrolysis. There would have been no reasonable expectation as to how antiviral activity would be affected by combining the teachings of Debnath and Vicente. The mechanism underlying Debnath's observations was unknown. Did hydrolysis of the carboranyl groups enhance antiviral activity? Was hydrolyzability perhaps essential to antiviral activity? Would preventing hydrolysis diminish or even destroy antiviral activity?

There would have been no way to predict the answers to these and similar questions with any reasonable degree of certainty. There would have been no reasonable

expectation of success in the proposed combination of references. Even if, hypothetically, such a combination might arguably have suggested an experiment that would have been "obvious to try," it would still be the case that there would have been no reasonable expectation of a successful outcome. With no reasonable expectation of success, the claimed inventions would not have been obvious. An experiment that is "obvious to try" is not an obvious invention under § 103 (except perhaps in the limited circumstance, not present here, where one skilled in the art is choosing from a finite number of identified, predictable solutions). See M.P.E.P. §§ 2143.02 and 2145, part (X)(B).

The March 20, 2008 Office Action said at page 7, "The advantages or disadvantages of hydrolysis of the carboranyl groups is irrelevant because Applicant has not establish a basis for what effect it might have or not have on HIV treatment."

With all respect, the Office's position implicitly, and impermissibly attempts to shift the burden of persuasion. There would have been no reasonable expectation of success, precisely because it was unknown how antiviral activity would be affected by hydrolyzable versus non-hydrolyzable carboranyl groups. The Office Action had faulted the Applicants' position, because the Applicants had not specified what effect hydrolysis would or would not have on the treatment . . . . But that is precisely the point: There would have been no reasonable basis for making such a prediction, because the consequences of the hydrolysis were entirely unknown. With no reasonable expectation of success, the invention could not have been obvious.

With all respect, the logic of the March 20, 2008 Office Action on this point was exactly backwards. The Office Action appeared to suggest that the burden is on the Applicants to demonstrate precisely what the effect of hydrolyzability would have been, and why the predicted effect would support the Applicants' position. The entire point, however, is that the effect could not have been predicted with any reasonable degree of certainty. Without a reasonable expectation of success, the claimed inventions would have been nonobvious.

If the Office should disagree, then it is the Office's burden, not the Applicants', to show what effect of hydrolyzability on antiviral activity would have been predicted, and why such a prediction could have been made with a reasonable degree of certainty.

§ 103 Paragraph Summary. It is respectfully submitted that the proposed combination of references would have had no reasonable expectation of success, that the claimed inventions would not have been obvious over the cited references, and that the § 103 rejection should be withdrawn.

Miscellaneous

The line corresponding to the Debnath *et al.* (1999) paper was not initialed by the Examiner on the copy of Applicants' November 11, 2003 Information Disclosure Citation that was received by the undersigned with the July 19, 2007 Office Action.

However, the Debnath *et al.* (1999) paper was one of the two references cited by the examiner in the § 103 rejection. Thus it is clear that the examiner has in fact considered the effect of this paper on the claimed inventions. So presumably this entry on the November 11, 2003 IDC was not initialed as the result of a simple clerical error.

Accordingly, and primarily to ensure the accuracy of the list of "References Cited" on the face of any patent to issue from this application, the Examiner is respectfully requested to initial the line corresponding to Debnath *et al.* (1999) on the IDC, and to return a copy of that page to the undersigned with the next communication concerning this application.

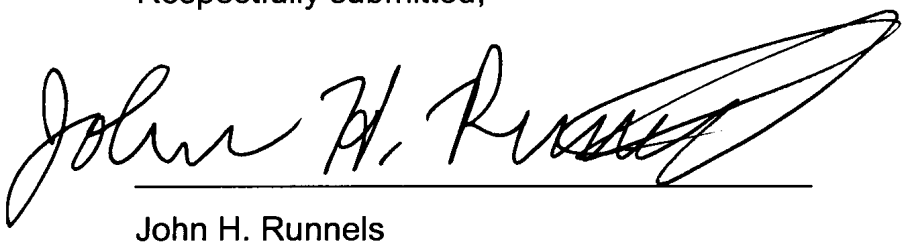
Conclusion

The full scope of all pending Claims should be examined.

The examiner is requested to return an updated copy of the November 11, 2003 IDC to the undersigned with the next communication concerning this application.

Allowance of Claims 1, 4-13, and 15-23 at an early date is respectfully requested.

Respectfully submitted,



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